November 5, 2010

Dear Chris,

I have made the following revisions to my paper as requested.

1. I was asked to re-format my paper to reach a non-specialist audience. To do this, I have weeded out technical language such as “kinetic and thermodynamic products.” It was recommended that I add a paragraph that provided a clear and more general overview. Instead, I have added small sections leading into each technical section (i.e: “Synthesis of the Nitro Pyrazole) to help the reader clearly the ties between green synthetic methods and Viagra’s synthesis. Here is an example: “The synthesis of nitro pyrazole **1** involves four key steps. The first two steps minimized waste production through different optimization techniques. Overall, the process involved green considerations related to chemical yields, safety hazards from reagents and solvent toxicity.”
2. I have proof-read my paper for logic errors. I did not correct the examples provided, as these sentences were irrelevant to my introduction and therefore deleted.
3. With respect to figures, I have simplified the captions provided in addition to correcting the errors in figure 2.
4. In addition to these suggestions, I have improved my introduction to focus on waste in the pharmaceutical industry and re-defined why Viagra is a good candidate for a case study (“As Viagra reduced the amount of organic waste produced from 1300L/kg to 7L/kg during its development, it was an ideal candidate for analysing green synthetic methods”)
5. I have added additional figures to clarify a few other points (see Figures 4 and 8).
6. I have added a section to comprehensively analyse Viagra’s synthesis and its future targets (See “The Synthesis: Environmental Assessment and Future Targets.”)
7. I have condensed multiple sections in the paper, reduced wordiness, and revised my conclusion.

In general, I have revised my paper to reduce wordiness. I have provided more in-depth analysis on the synthesis and attempted to provide stronger links between the synthesis and green concepts. Thank you for your time and input.

Sincerely,

Carolyn L. Ladd

Viagra (Sildenafil Citrate): A Case Study in Developing Greener Synthesis

Carolyn L. Ladd

SCIE 311

November 5, 2010

Word Count: 1738

# Introduction

In 1998 Viagra (sildenafil citrate) was the first commercial drug approved for treating male erectile dysfunction and made more than 1 billion dollars its first year (Dunn et al. 2004). During the 1990’s, a typical pharmaceutical compound produced 50-100 kgs of waste per 1kg of product (Kümmerer 2010). These statistics highlighted a need for greener synthetic methods in the pharmaceutical industry. As Viagra reduced the amount of organic waste produced from 1300L/kg to 7L/kg during its development, it was an ideal candidate for analysing green synthetic methods (Dunn et al. 2004).Viagra’s synthesis will be assessed based on toxicity, quality and quantity of the solvents and reagents in addition to green metrics such as atom economy, chemical yields and Sheldon’s E-factor

# Components of an Ideal Green Synthesis

To properly assess the synthesis of Viagra, the criteria for a “green process” must first be defined. These criteria can be either qualitative or quantitative. Qualitative criteria include toxicity and type of solvents and reagents, whereas, quantitative criteria involve “green metrics,” or methods used to quantify “greenness” (Constable et al. 2002). The key green metrics to be discussed include atom economy, E-factor, and chemical yields.

Developed by Barry Trost, atom economy describes to what extent the reactants are integrated into the product (**Figure 1**) (Constable et al. 2002). A reaction with good atom economy incorporates all reactant atoms into its product, eliminating the production of waste.



**Figure 1. The equation for calculating atom economy.**

As Figure 2 illustrates, examples of ideal atom economy include cycloaddition (**a**) and rearrangement reactions (**b**) (Trost 1995), whereas poor atom economical reactions include elimination (**c**) and substitution reactions (**d**) (Curzons et al.2001). Through using high atom economical reactions, waste by-products can be minimized or avoided. (Tucker 2006).



**Figure 2. Examples of good atom economy vs. poor atom economy. The red boxes indicate waste by-products.**

E-factor was introduced by Roger Sheldon and is a ratio of the total waste to the total mass of product as Figure 3 illustrates (Constable et al. 2002).

**Figure 3. Equation for the calculation of E-factor.**

|  |  |  |
| --- | --- | --- |
| **Industry** | **Tonnage** | **E-Factor** |
| Bulk Chemicals | 104-106 | less than 1 to 5 |
| Fine Chemicals | 102-104 | 5 to 50 |
| Pharmaceuticals | 10-103 | 25 to 100 |

**Table 1. E-factors and tonnage produced by industry (Sheldon 2005).**

A low E-factor is desirable as this indicates that a minimal quantity of waste is produced at the expense of product. As Table 1 shows, pharmaceuticals have the highest E-factor, 25-1000 kg of waste per kg of product compared to other industries. This is because complex compounds with high purity standards must be produced (Dunn et al. 2004).

When assessing solvents and reagents, both the toxicity and quantity must be considered. It is important to reduce both solvent amounts and the number of solvent types. Because a multiple solvent system requires energy input for solvent recovery, it is greener to use the same solvent for an entire process (Curzons et al. 2001). In terms of solvent quantity, 83% of 88 million kg of pharmaceutical waste resulted from solvents in 2008, indicating how minimizing solvent use can significantly impact the quantity of waste produced (Raymond et al. 2010).

Unfavourable solvents encompass two classes: halogenated solvents and polar aprotic solvents (**Table 2**). Halogenated solvents are highly toxic, whereas polar aprotic solvents are high boiling and difficult to remove (Sheldon 2005). Polar aprotic solvents are also slightly soluble in water, creating water contamination issues.



**Table 2. Acceptable solvents and solvents to avoid.**

Chemical reagents can be stoichiometric or catalytic. Catalysts are preferred as they are re-useable, energy efficient and produce less waste compared to their stoichiometric counterparts (Anastas et al. 2001). Stoichiometric reagents are single use and produce waste by-products (**Figure 4**) (Sheldon 2005).



**Figure 4. The use of stoichiometric reagents vs. catalytic reagents. The orange box indicates waste by-products resulting from single-use stoichiometric reagents.**

Syntheses should be designed to utilize non-toxic solvents and reagents for worker safety and to prevent toxic chemical releases into the environment. An ideal synthesis should have good atom economy and high chemical yields, and the overall process should have a low E-factor. Catalytic processes should be used preferentially to stoichiometric ones and single solvents should be used over multiple solvents. Adapting these methods produces reduced cost, reduced waste, improved safety and reduced energy inputs. These concepts will be addressed with respect to the synthesis of Viagra.

# The Synthetic Approach to Viagra (sildenafil citrate)

Viagra (sildenafil citrate) is synthesized from two key components: nitro pyrazole **1** and sulphonamide **2** (Dunn et al. 2004). Both components are fused together and cyclised to form sildenafil, **3** which is then converted to its citrate salt (**Figure 5)**. The individual syntheses of **1** and **2** will be outlined below and will be assessed for their individual reactions and commercial scale-up. Common themes that will be observed involve minimizing by-product waste, altering reactions to prevent safety hazards, and changing solvent and reagent toxicity.



**Figure 5. A simplified synthetic overview of Viagra. 1 and 2 are synthesized separately, and then coupled to form desired product, 3.**

# Synthesis of the Nitro Pyrazole

The synthesis of nitro pyrazole **1** involves four key steps. The first two steps minimized waste production through different optimization techniques. Overall, the process involved green considerations related to chemical yields, safety hazards from reagents and solvent toxicity.

The first step involves reacting 2-pentanone (**5)** and diethyl oxalate (**4)**, producing water as a by-product **(Figure 6)** (Dunn 2005). As this reaction can form two products **6** and **7**, the reaction was optimized to increase the ratio of desired product **(7)** to undesired product **(6)** (Dunn (2005). Using 2-pentanone **(5)** over 2-butanone increased the ratio from 1:1 to 8:1 and maintaining a temperature of 40°C for several hours increased the ratio from 8:1 to 98:2. Through altering reaction conditions, less unwanted product is formed, producing less waste.



**Figure 6. The condensation between diethyl oxalate (4) and 2-pentanone (5). 6 and 7 represent the undesired and desired products respectively.**

The next step formed pyrazole **9** using methyl hydrazine which also formed two products,desired product **8** and undesired product **9** (**Figure 7)**.



**Figure 7. The route to obtain desired product 8 and undesired product 9.**

This time optimization involved altering how the reactants were added. When **7** was added to ethanol and methylhydrazine **(a)** instead of adding methylhydrazine and ethanol to **7 (b)** , the desired product (**8**) was formed preferentially (10:1 vs. 4:5) (**Figure 8)** (Dunn 2005).



**Figure 8. Optimization via changing the order of addition. Method (a) formed the desired product preferentially compared to (b).**

The benefits for this reaction are the decent chemical yield (78.3%) and the use of ethanol as less toxic solvent (Dunn 2005). However, this reaction has a poor atom economy due to by-product formation and requires energy input to remove by-products. Methylhydrazine is also a highly toxic and dangerous reagent.

The final steps in pyrazole synthesis involve nitration, then ammonolysis (**Figure 9**). Anhydrous nitric acid in anhydrous sulphuric acid nitrated the pyrazole with good conversion (97%) (Dunn 2005). Despite the efficient conversion to product, this step posed safety concerns resulting from using large amounts of sulphuric acid. Additionally, high temperatures cause the acid to decompose, producing CO2 gas. This increased pressure from CO2 risked a potential explosion (Dale et al. 2000). Consequently, this reaction was broken into several steps for slow energy release, avoiding high temperatures. Methanolic ammonia converted the nitro ester to the amide rendering pyrazole **1** with 98% yield.



**Figure 9. The conversion from pyrazole 8 to the nitro pyrazole, 1. Step one adds a nitro group as indicated in blue and step 2 converts the ester to an amide as indicated in red.**

In general, the synthesis of **1** utilized non-toxic solvents except for the acid used in the nitration. The last two steps were the most efficient based on high chemical yields, whereas the first steps needed optimization to minimize by-products. Replacing these first two steps with 100% atom economical reactions would improve the synthetic efficiency and minimize waste production, while using a less dangerous alternative to methylhydrazine would improve the safety for synthesizing **1.**

# Synthesis of the Sulphonamide

In the one-step synthesis of sulphonamide **2,** issues involvingsolvent and reagent toxicity, yield and atom economy were identified.

**2** isprepared from 2-ethoxy-benzoic acid using thionyl chloride (SOCl2 **)** and chlorosulfuric acid (ClSO3H) **(Figure 10)** (Dale et al. 2000). This reaction has a decent atom economy of 74% however only has a product yield of 68% (Dunn et al. 2004). Additionally, SOCl2 and ClSO3H are both dangerously reactive and create extensive amounts of aqueous and salt waste from quenching. Quenching is when excess reagents are converted to a non-reactive form, often using water.

The sulphonamide was isolated as unwanted salt **12,** however, changing the solvent to water produced desired product **13**. It was therefore beneficial for both the reaction and the environment to use water instead of toxic organic solvents such as triethylamine.



**Figure 10. The synthesis of sulphonamide 13. Using water as a solvent prevents the formation of 12.**

During commercial scale-up, it was discovered that only minimal SOCl2 was needed compared to the earlier amounts used. In addition to improving safety conditions, this change allowed the use of a catalytic process later because excess SOCl2 had previously poisoned the catalyst (Dunn et al. 2004).

The synthesis of sulphonamide utilizes benign solvents, however, also produces extensive amounts of aqueous waste and uses dangerous reagents. The atom economy and chemical yield are mediocre; nevertheless, this reaction does allow the sulphonamide to be produced in a single step, which produces less waste compared to a multi-step synthesis.

# Hydrogenation, Coupling, and Cyclisation: Final Steps towards Viagra

Once synthesized, sulphonamide **2** and nitro pyrazole **1** are reacted together through a three-step one-pot reaction sequence (**Figure 11)**. This sequence was analysed for its atom economy, chemical yields and toxicity of solvents and reagents.

The first transformation converts **1** to an amide using Pd/C as a catalyst with both good atom economy (83%) and yield (100%) (Dunn et al. 2004). This step represents a green reaction as the catalyst and solvent can both be recovered. This was a greener alternative from the previous method which used tin chloride, a heavy metal reagent that produced toxic by-products (Dale et al. 2000).

The next step coupled **1** and **2** together using N,N’-carbonyldiimidazole (CDI). This special coupling reagent allowed for single solvent usage and easy solvent recovery, produced no aqueous waste, and required low energy inputs. An atom economy of 73% was obtained with a 90% yield (Dunn et al. 2004).

The final step involved refluxing the product in tert-butanol (t-BuOH) and potassium tert-butoxide (t-BuOK). This gave sildenafil in 100% yield with a good atom economy of 83%. This improved the previous method which used sodium hydroxide and hydrogen peroxide, a corrosive and explosive substance (Dunn et al. 2004). Using tert-butanol presented a downside for this reaction, as its water solubility made solvent recovery difficult. Dunn forecasts that t-BuOH will be switched to a recoverable solvent, reducing solvent waste from 7L/kg to 4L/kg (2004).

As a general sequence, combining all three reactions into one-pot reduced waste, utilized a less toxic solvent ,ethyl acetate, and eliminated previous toxic and safety hazards from tin and hydrogen peroxide. A discussion of the overall environmental assessment for Viagra will be presented below.



## Cyclisation

## Hydrogenation

## Coupling

**Figure 11. The three reaction sequence, hydrogenation, coupling and cyclisation to produce sildenafil. Using CDI (N,N’-carbonyldiimidazole) allows a single less toxic solvent, EtOAc to be used for all three reactions.**

# The Synthesis: Environmental Assessment and Future Targets

Viagra’s synthesis has lessened its environmental impact over the years. For example, the amount of organic waste has decreased from 1300L/kg to 7L/kg with future targets set at 4L/kg (Dunn et al. 2004). This waste consisted of six different types of solvent waste including dichloromethane, a volatile halogenated compound. Presently, only four types of solvent waste are produced, with the majority stemming from less toxic solvents such as ethyl acetate.

For atom economy, the overall process has stayed constant at 54%; however, the yield has increased from 36% to 75%. Future targets aim to increase the yield to 82% while maintaining the atom economy (Dunn et al. 2004). Increasing the yield will make these reactions more efficient and reduce waste.

Of significance, the E-factor for Viagra is 6, meaning this process produces less waste compared to most pharmaceutical processes (25-1000). As a result of these reductions, Pfizer received a UK award for Green Chemical technology for the Viagra process in 2003 (Dunn et al. 2004).

# Conclusion

The synthesis of Viagra illustrates how small changes to a chemical process can have large impacts environmentally. Through waste reduction, high chemical yields, good atom economy and solvent and reagent considerations, pharmaceuticals can improve synthetic efficiency and low their environmental impact. Green methods provide a means for preventing chemical waste and a way for pharmaceuticals industry to develop an environmentally-friendly image

# Literature Cited

## Research Articles

Anastas P, Kirchhoff M, Williamson T. 2001. Catalysis as a foundational pillar of green chemistry. Applied Catalysis A: General. 221: 3-13.

Constable D, Curzons A, Cunningham V. 2002. Metrics to ‘green’ chemistry—which are the best? Green Chemistry. 4: 521-527.

Dale D, Dunn P, Golightly C, Hughes M, Levett P, Pearce A, Searle P, Ward G, Wood A. 2000. The chemical development of the commercial route to sildenafil: a case history. Organic Process Research and Development. 4(1): 17-22.

Dunn P, Galvin S, Hettenbach K. 2004. The development of an environmentally benign synthesis of sildenafil citrate (Viagra) and its assessment by Green Chemistry metrics. Green Chemistry. 6: 43-48.

Raymond M, Slater CS, Savelski M. 2010. LCA approach to the analysis of solvent waste issues in the pharmaceutical industry. Green Chemistry. 12: 1826-1834.

Tucker J. 2006. Green chemistry, a pharmaceutical perspective. Organic Process Research & Development. 10 (2):315-319.

## Reviews

Curzons A, Constable D, Mortimer D, Cunningham V. 2001. So you think your process is green, how do you know?—using principles of sustainability to determine what is green—a corporate perspective. Green Chemistry. 3:1-6.

Dunn P. 2005. Synthesis of commercial phosphodiesterase (V) inhibitors. Organic Process Research and Development. 9(1): 88-97.

Kümmerer K. 2010. Pharmaceuticals in the environment. Annual Review of Environment and Resources. 35:57-75.

Sheldon, R. 2005. Greener solvents for sustainable organic synthesis: state of the art. Green Chemistry. 7: 267-278.

Trost B. 1995. Atom economy—a challenge for organic synthesis: homogeneous catalysis leads the way. Angewandte Chemie International Edition.34:259-281.